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Chiral α-Amino Phosphonates via Rhodium-Catalyzed Asymmetric 1,4-Addition Reactions

Nicolas Lefevre,[†] Jean-Louis Brayer,[‡] Benoît Folléas,[‡] and Sylvain Darses*[,†]

Ecole Nationale Supérieure de Chimie de Paris, Laboratoire Charles Friedel (UMR 7223, CNRS), 11 rue Pierre et Marie Curie, 75231 Paris cedex 05, France, and Diverchim, ZAC du Moulin, 6 rue du Noyer, 95700 Roissy-en-France, France

sylvain-darses@chimie-paristech.fr

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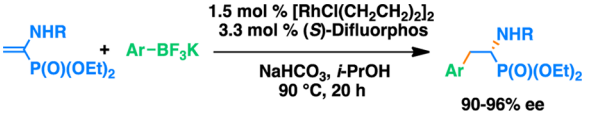
ABSTRACT



A new approach for the preparation of enantioenriched α-amino phosphonates and derivatives is described. Indeed, the rhodium-catalyzed asymmetric 1,4-addition of potassium organotrifluoroborates to dehydroaminophosphonates afforded α-amino phosphonates in good yields and high enantioselectivities (up to 96%) using Difluorphos as a chiral ligand.

Optically active α-amino phosphonic acids and derivatives are important synthetic intermediates used in the pharmaceutical and agrochemical industries to prepare target molecules such as peptides, proteins, or even many natural products.[1] These are analogues of α-amino acids[2] in which the carboxylic acid group has been substituted with a phosphonic acid group. Among the chiral phosphonic acids described, some have been isolated from natural products and possess various biological activities: antiviral, antifungal, herbicides, or anti-HIV.[1,3] In the synthesis of such compounds, it is important to control the absolute configuration of the α-stereogenic center because the biological properties of the products are correlated: for example (*R*)-1-phospholeucine is a better inhibitor of leucine peptidase than the (*S*)-isomer.[1]

Several methods have been described for the preparation of enantiomerically enriched α-amino phosphonic acids derivatives.[1] Most of the strategies employed involve the formation of a new carbon–hydrogen, carbon–phosphorus, carbon–carbon, or carbon–nitrogen bond. While many reactions using stoichiometric chiral auxiliaries have been described,[4] catalytic approaches are scarcer. Asymmetric hydrogenation of unsaturated substrates is a first

[†] Ecole Nationale Supérieure de Chimie de Paris.
[‡] Diverchim.

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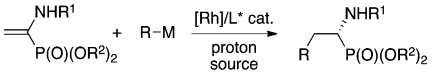
approach for the formation of enantiomerically enriched α-amino phosphonates.[5−8] Enantioselectivities up to 96% have been achieved, but the preparation of substrates is not obvious. Another approach has been described by Jørgensen and co-workers via the asymmetric catalytic electrophilic amination (C−N bond formation) of a β-ketophosphonate with dibenzyl azodicarboxylate in the presence of a zinc(II) complex and a chiral bisoxazoline.[9] The addition of nucleophiles to α-imino phosphonates, in the presence of chiral catalysts, also provides access to enantiomerically enriched α-amino phosphonates via C−C bond formation.[10] However, the most effective approach is currently the catalytic hydrophosphonylation of imines.[11] This reaction has been first described by Shibasaki and co-workers in 1995 and is catalyzed by chiral lanthanide complexes.[12] Other chiral catalysts have since been developed, mainly Brønsted acids[13] or aluminum and others complexes.[14]

We report here for the first time a straightforward and alternative approach for the preparation of enantioenriched α-amino phosphonates via the asymmetric rhodium-catalyzed addition of organoboron derivatives to dehydroaminophosphonates (Scheme 1).

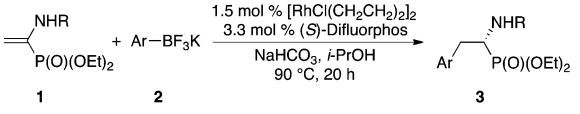
Scheme 1. Chiral α-Amino Phosphonates from Rhodium-Catalyzed Asymmetric 1,4-Addition Reactions



We previously reported that the conjugate addition of potassium trifluoro(organo)borates[15] to dehydroalanine derivatives, catalyzed by a chiral rhodium catalyst, afforded an access to a variety of protected α-amino esters with high yields and enantiomeric excesses up to 95%.[16] Under these conditions, that is in the presence of a rhodium catalyst associated with Difluorphos ligand and using guaiacol as proton source, moderate conversion (66%) and enantioselectivity (76%) were observed. The use of other chiral ligands did not result in any improvement.

After several optimizations, we were pleased to find that by using $[RhCl(CH_2CH_2)_2]_2$ as a rhodium catalyst precursor and Difluorphos as a chiral ligand, but with isopropanol as solvent and $NaHCO_3$ as base, α-amino phosphonates were obtained cleanly with improved yields and high levels of enantioselecivity (Scheme 2).

Scheme 2. Enantioenriched α-Amino Phosphonates via Rhodium-Catalyzed Addition/Protonation



R = Ac (**1a**), COPh (**1b**)
Ar = C_6H_5 (**2a**), 4-FC_6H_4 (**2b**), 4-ClC_6H_4 (**2c**), 3-ClC_6H_4 (**2d**), 4-$CF_3C_6H_4$ (**2e**), 3-$CF_3C_6H_4$ (**2f**), 4-*t*-BuC_6H_4 (**2g**), 4-$MeOC_6H_4$ (**2h**), 3-$MeOC_6H_4$ (**2g**)

Indeed, the addition of potassium phenyltrifluoroborate (**2a**) to dehydroaminophosphonate **1a** occurred smoothly at 90 °C, providing the enantioenriched α-amino phosphonate **3aa** with an enantiomeric excess of 94% (Table 1, entry 1). The other enantiomer was easily obtained, with the same level of enantioselectivity, using (*R*)-Difluorphos as the ligand (entry 2). In order to determine the absolute configuration, the known α-amino phosphonate **3ba** was prepared via the addition of potassium phenyltrifluoroborate to dehydroaminophosphonate **1b**. The 1,4-addition product

Table 1. Rhodium-Catalyzed Addition of Potassium Aryltrifluoroborates to Dehydroaminophosphonates[a]

entry	1	$ArBF_3K$	yield[b] (%)	ee[c] (%)
1	**1a**	**2a**	91 (**3aa**)	94 (−)
2[d]	**1a**	**2a**	65 (**3aa**)	96 (+)
3	**1b**	**2a**	69 (**3ba**)	92 (*R*)
4	**1a**	**2b**	65 (**3ab**)	92 (−)
5	**1a**	**2c**	72 (**3ac**)	93 (−)
6	**1a**	**2d**	80 (**3ad**)	94 (−)
7	**1a**	**2e**	86 (**3ae**)	94 (−)
8	**1a**	**2f**	84 (**3af**)	94 (−)
9	**1a**	**2g**	76 (**3ag**)	91 (−)
10	**1a**	**2h**	51 (**3ah**)	94 (−)
11	**1a**	**2i**	77 (**3ai**)	90 (−)

[a] Reactions conducted on 0.34 mmol of **1**, 2 equiv of **2**, 1 equiv of $NaHCO_3$, 1.5 mol % of $[RhCl(CH_2CH_2)_2]_2$, and 3.3 mol % of (*S*)-Difluorphos, in isopropanol at 90 °C for 20 h. [b] Isolated yields. [c] Determined by chiral HPLC analysis (see Supporting Information). The sign of the optical rotation or absolute configuration for known compounds is shown in parentheses. [d] Using (*R*)-Difluorphos as a chiral ligand.

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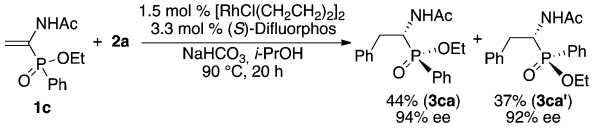
Scheme 3. Preparation of Enantioenriched α-Amino Phosphinates



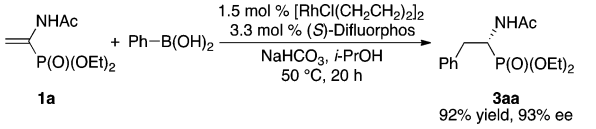
was obtained in 69% yield and with an enantiomeric excess of 92% and proved to be in the (*R*) configuration.[5]

Diversely substituted enantioenriched α-amino phosphonates were readily obtained using this tandem carbometalation/enantioselective protonation process (entries 4−11) with high levels of enantioselectivities (above 90%) whatever the substitution pattern on the aryltrifluoroborate moiety.

These reaction conditions are not limited to the preparation of enantioenriched α-amino phosphonates. Indeed, under identical conditions, the addition of potassium phenyltrifluoroborate (**1a**) to **1c** afforded good yields of diastereoisomeric α-amino phosphinates **3ca** and **3ca′** (Scheme 3) with nearly identical enantiomeric excesses (94% and 92% respectively). This result suggests that the chiral center on the phosphorus atom did not influence the chirality of the newly created chiral carbon center. Single-crystal X-ray diffraction of **3ca** confirmed the (*R,R*) configuration of this isomer (see Supporting Information).

These conditions were also suitable for the addition of arylboronic acids, but with a somewhat lower enantioselectivity. For example, the rhodium-catalyzed asymmetric addition of phenylboronic acid to **1a** afforded α-amino phosphonate **3aa** in 92% yield and 93% ee (Scheme 4).

Scheme 4. Enantioenriched α-Amino Phosphonates from Boronic Acids



We have developed a new and straightforward method to access enantioenriched, useful α-amino phosphonate and phosphinate derivatives using rhodium-catalyzed asymmetric 1,4-addition of potassium organotrifluoroborates to dehydroaminophosphorous compounds. This simple procedure would allow the fast generation of libraries of such compounds with useful levels of enantioselectivity.

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Supporting Information Available. Experimental procedures, description of the compounds, and X-ray diffraction of **3ca**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.